

**INFLUENZA VIRUS VACCINE
(FLUVIRIN®)**

Purified Surface Antigen Vaccine
2006-2007 FORMULA

DESCRIPTION

Influenza Virus Vaccine, **FLUVIRIN®** (Surface Antigen) is a sterile parenteral for intramuscular use only. It is a purified split-virus preparation. The vaccine is a slightly opalescent liquid.

FLUVIRIN® is prepared from the extraembryonic fluid of embryonated chicken eggs inoculated with a specific type of influenza virus suspension containing neomycin and polymyxin. The fluid containing the virus is harvested and clarified by centrifugation and filtration prior to inactivation with betapropiolactone. The inactivated virus is concentrated and purified by zonal centrifugation. The surface antigens, hemagglutinin and neuraminidase, are obtained from the influenza virus particle by further centrifugation in the presence of Nonylphenol Ethoxylate, a process which removes most of the internal proteins. The Nonylphenol Ethoxylate is removed from the surface antigen preparation and the antigens are suspended in 0.01M phosphate buffered saline. The hemagglutinin content is standardized according to current US Public Health Service requirements. Each 0.5 mL contains the recommended ratio of 15µg each of A/Wisconsin/67/2005 NYMC X-161; A/New Caledonia/20/99 IVR-116; B/Malaysia/2506/2004 hemagglutinin antigens.

Thimerosal (mercury derivative, ≤0.98 mcg mercury per 0.5 mL dose) is used in manufacture of the unit dose preservative free presentation but is reduced by the purification process to trace amounts. Polymyxin, neomycin, and betapropiolactone cannot be detected in the final product by current assay procedures. This vaccine is manufactured and released by Chiron Vaccines Limited in the UK.

CLINICAL PHARMACOLOGY

Influenza A and B are the two types of influenza viruses that cause epidemic human disease. Influenza A viruses are further categorized into subtypes based on two surface antigens: hemagglutinin (H) and neuraminidase (N). Influenza B viruses are not categorized into subtypes. Since 1977, influenza A (H1N1) viruses, influenza A (H3N2) viruses, and influenza B viruses have been in global circulation. In 2001, influenza A (H1N2) viruses that probably emerged after genetic reassortment between human A (H3N2) and A (H1N1) viruses began circulating widely. Both influenza A and B viruses are further separated into groups on the basis of antigenic characteristics. New influenza virus variants result from frequent antigenic change (i.e. antigenic drift) resulting from point mutations that occur during viral replication. Influenza B viruses undergo antigenic drift less rapidly than influenza A viruses. A person's immunity to the surface antigens, including hemagglutinin, reduces the likelihood of infection and severity of disease if infection occurs. Antibody against one influenza virus type or subtype confers limited or no protection against another. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the usual incorporation of one or more new strains in each year's influenza vaccine.¹

Clinical signs and symptoms of influenza

Influenza viruses are spread from person-to-person primarily through the coughing and sneezing of infected persons. The incubation period for influenza is 1-4 days with an average of 2 days. Adults typically are infectious from the day before symptoms begin through approximately 5 days after illness onset. Children can be infectious for ≥ 10 days, and young children can shed virus for ≤ 6 days before their illness onset. Severely immunocompromised persons can shed virus for weeks or months.¹ Uncomplicated influenza illness is characterized by the abrupt onset of constitutional and respiratory signs and symptoms (e.g., fever, myalgia, headache, severe malaise, nonproductive cough, sore throat and rhinitis). Among children, otitis media, nausea and vomiting are also commonly reported with influenza illness.¹

Respiratory illness caused by influenza is difficult to distinguish from illness caused by other respiratory pathogens on the basis of symptoms alone. Reported sensitivities and specificities of clinical definitions for influenza-like illness in studies primarily among adults that include fever and cough have ranged from 63% to 78% and 55% to 71%, respectively, compared with viral culture. Sensitivity and predictive value of clinical definitions can vary, depending on the degree of co-circulation of other respiratory pathogens and the level of influenza activity.

A study among older nonhospitalized patients determined that symptoms of fever, cough, and acute onset had a positive predictive value of 30% for influenza, whereas a study of hospitalized older patients with chronic cardiopulmonary disease determined that a combination of fever, cough and illness of < 7 days was 78% sensitive and 73% specific for influenza.¹ However, a study among vaccinated older persons with chronic lung disease reported that cough was not predictive of influenza infection, although having a fever or feverishness was 68% sensitive and 54% specific for influenza infection.¹

Influenza illness typically resolves after a limited number of days for the majority of persons, although cough and malaise can persist for > 2 weeks. Among certain persons, influenza can exacerbate underlying medical conditions (e.g., pulmonary or cardiac disease), lead to secondary bacterial pneumonia or primary influenza viral pneumonia, or occur as part of a co-infection with other viral or bacterial pathogens.¹ Young children with influenza infection can have initial symptoms mimicking bacterial sepsis with high fevers, and $\leq 20\%$ of children hospitalized with influenza can have febrile seizures.¹ Influenza infection has also been associated with encephalopathy, transverse myelitis, Reye syndrome, myositis, myocarditis, and pericarditis.¹

Hospitalizations and deaths from influenza

The risks for complications, hospitalization, and deaths from influenza are higher among persons aged ≥ 65 years, very young children, and persons of any age with certain underlying health conditions than among healthy older children and younger adults. Estimated rates of influenza-associated hospitalizations have varied substantially by age group in studies conducted during different influenza epidemics.¹

Among children aged 0-4 years, hospitalization rates have ranged from approximately 500 per 100,000 population for those with high-risk medical conditions to 100 per 100,000 population for those without high-risk medical conditions. Within the 0-4 age group, hospitalization rates are highest among children aged 0-1 years and are comparable to rates found among persons ≥ 65 years.¹

During influenza epidemics from 1969-1970 through 1994-1995, the estimated overall number of influenza-associated hospitalizations in the United States has ranged from approximately 16,000 to 220,000 per epidemic. An average of approximately 114,000 influenza-related excess hospitalizations occurred per year, with 57% of all hospitalizations occurring among persons aged <65 years. Since the 1968 influenza A (H3N2) virus pandemic, the greatest numbers of influenza-associated hospitalizations have occurred during epidemics caused by type A (H3N2) viruses, with an estimated average of 142,000 influenza-associated hospitalizations per year.¹

Influenza-related deaths can result from pneumonia as well as from exacerbations of cardiopulmonary conditions and other chronic diseases.

Older adults account for $\geq 90\%$ of deaths attributed to pneumonia and influenza.¹ In a recent study of influenza epidemics, approximately 19,000 influenza-associated pulmonary and circulatory deaths per influenza season occurred during 1976-1990, compared with approximately 36,000 deaths during 1990-1999.¹ Estimated rates of influenza-associated pulmonary and circulatory deaths per 100,000 persons were 0.4-0.6 among persons aged 0-49 years, 7.5 among persons aged 50-64 years, and 98.3 among persons aged ≥ 65 years.¹ In the United States, the number of influenza-associated deaths might be increasing in part because the number of older persons is increasing.¹ In addition, influenza seasons in which influenza A (H3N2) viruses predominate are associated with higher mortality;¹ influenza A (H3N2) viruses predominated in 90% of influenza seasons from 1990-1999, compared with 57% of seasons from 1976-1990.¹ Deaths from influenza are uncommon among children with and without high risk conditions, but do occur.¹ A study that modeled influenza-related deaths estimated that an average of 92 deaths occurred among children aged <5 years annually during the 1990's compared with 35,274 deaths among adults aged ≥ 50 years.¹ Preliminary reports of laboratory-confirmed pediatric deaths during the 2003-04 influenza season indicated that among these 143 influenza-related deaths (as of April 10, 2004), 58 (41%) were aged <2 years and, of those aged 2-17 years, 65 (45%) did not have an underlying medical condition traditionally considered to place a person at risk for influenza-related complications.¹ Further information is needed on the risk of severe influenza-complications and optimal strategies for minimizing severe disease and death among children.¹

Options for controlling influenza

In the United States, the primary option for reducing the impact of influenza is immunoprophylaxis with vaccine. Vaccinating persons at high risk for complications and their contacts each year before seasonal increases in influenza virus circulation is the most effective means of reducing the effect of influenza. Vaccination coverage can be increased by administering vaccine to persons during hospitalizations or routine health-care visits before the influenza season, making special visits to physicians' offices or clinics unnecessary. When vaccine and epidemic strains are well matched, achieving increased vaccination rates among persons living in closed settings (e.g., nursing homes and other chronic care facilities) and among staff can reduce the risk for outbreaks by inducing herd immunity. Vaccination of health care workers and other persons in close contact with persons at increased risk for severe influenza illness can also reduce transmission of influenza and subsequent influenza-related complications.¹

Antiviral drugs used for chemoprophylaxis or treatment of influenza are a key adjunct to vaccine. However, antiviral medications are not a substitute for vaccination.

Influenza Vaccine Composition

Inactivated influenza vaccine contains the hemagglutinins of strains (i.e., typically two type A and one type B), representing the influenza viruses likely to circulate in the United States during the 2006-2007 influenza season. The vaccine viruses are made noninfectious (i.e., inactivated or killed).¹ Because the vaccine viruses are initially grown in embryonated hens' eggs, the vaccine might contain limited amounts of residual egg protein. Inactivated influenza vaccine distributed in the United States also contains thimerosal, a mercury-containing compound, as the preservative.

Efficacy and Effectiveness of Inactivated Influenza Vaccine

The effectiveness of influenza vaccine depends primarily on the age and immunocompetence of the vaccine recipient and the degree of similarity between the viruses in the vaccine and those in circulation. The majority of vaccinated children and young adults develop high postvaccination hemagglutination inhibition antibody titers. These antibody titers are protective against illness caused by strains similar to those in the vaccine.¹

Adults aged <65 Years. When the vaccine and circulating viruses are antigenically similar, influenza vaccine prevents influenza illness in approximately 70%-90% of healthy adults aged <65 years. Vaccination of healthy adults also has resulted in decreased work absenteeism and decreased use of health care resources, including the use of antibiotics, when the vaccine and circulating viruses are well matched.

Children. Children aged as young as 6 months can develop protective levels of antibody after influenza vaccination although the antibody response among children at high risk of influenza-related complications might be lower than among healthy children. In a randomized study among children aged 1-15 years, inactivated influenza vaccine was 77%-91% effective against influenza respiratory illness and was 44%-49%, 74%-76%, and 70%-81% effective against influenza seroconversion among children aged 1-5, 6-10, and 11-15 years, respectively. One study reported a vaccine efficacy of 56% against influenza illness among healthy children aged 3-9 years, and another study determined vaccine efficacy of 22%-54% and 60%-78% among children with asthma aged 2-6 years and 7-14 years respectively. A 2 year randomized study of children aged 6-24 months determined that $\geq 89\%$ of children seroconverted to all three vaccine strains during both years. During year 1, among 411 children, vaccine efficacy was 66% (95% confidence interval [CI] = 34% and 82%) against culture-confirmed influenza (attack rates: 5.5% and 15.9% among vaccine and placebo groups, respectively). During year 2, among 375 children, vaccine efficacy was -7% (95% CI = -247% and 67%; attack rates: 3.6% and 3.3% among vaccine and placebo groups, respectively; the second year exhibited lower attack rates overall and was considered a mild season). However no overall reduction in otitis media was reported. Other studies report that trivalent inactivated influenza vaccine decreases the incidence of influenza-associated otitis media among young children by approximately 30%.¹

Adults aged ≥ 65 years of Age. Older persons and persons with certain chronic diseases might develop lower post-vaccination antibody titers than healthy young adults and thus can remain susceptible to influenza-related upper respiratory tract infection. A

randomized trial among noninstitutionalized persons aged ≥ 60 years reported a vaccine efficacy of 58% against influenza respiratory illness, but indicated that efficacy might be lower among those aged ≥ 70 years.¹ The vaccine can also be effective in preventing secondary complications and reducing the risk for influenza-related hospitalization and death among adults ≥ 65 years with and without high-risk medical conditions (e.g. heart disease and diabetes). Among elderly persons not living in nursing homes or similar chronic-care facilities, influenza vaccine is 30%-70% effective in preventing hospitalization for pneumonia and influenza. Among older persons who do reside in nursing homes, influenza vaccine is most effective in preventing severe illness, secondary complications, and deaths. Among this population the vaccine can be 50%-60% effective in preventing hospitalization or pneumonia and 80% effective in preventing death, although the effectiveness in preventing influenza illness often ranges from 30%-40%.¹

INDICATIONS AND USAGE

***FLUVIRIN®** is indicated for immunization against the influenza virus strains contained in the vaccine for use in the United States for persons of 4 years of age and older.*

Even when the current influenza vaccine contains one or more antigens administered in previous years, annual vaccination with the current vaccine is necessary because immunity declines in the year following vaccination.¹ Vaccine prepared for a previous influenza season should not be administered to provide protection for the current season.¹

Target Groups For Vaccination

Persons at increased risk for complications

Vaccination with inactivated influenza vaccine is recommended for the following persons who are at increased risk for complications from influenza (see **PRECAUTIONS**,

Pediatric Use, Geriatric Use).

1. Persons aged ≥ 65 years.¹
2. Residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions.¹
3. Adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma.¹
4. Adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus [HIV]).¹
5. Children and adolescents (aged 6 months to 18 years) who are receiving long-term aspirin therapy and therefore might be at risk for experiencing Reye syndrome after influenza infection.¹ Note, **FLUVIRIN®** is not indicated for use in children under 4 years of age.
6. Women who will be pregnant during the influenza season.¹ **Refer to IMMUNIZATION OF OTHER GROUPS for use of this product in pregnant women.**

In 2000, approximately 73 million persons in the United States were included in one or more of these target groups, including 35 million persons aged ≥ 65 years; and 12 million adults aged 50-64 years, 18 million adults aged 18-49 years, and 8 million children aged 6 months-17 years with one or more medical conditions that are associated with an increased risk for influenza-related complications.¹

Persons Aged 50-64 Years

Vaccination is recommended for persons aged 50-64 years because this group has an increased prevalence of persons with high risk conditions. In 2000, approximately 42 million persons in the United States were aged 50-64 years of whom 12 million (29%) had one or more high-risk medical conditions. Influenza vaccine has been recommended for this entire age group to increase the low vaccination rates among persons in this age group with high-risk conditions. Age-based strategies are more successful in increasing vaccine coverage than patient-selection strategies based on medical conditions. Persons aged 50-64 years without high-risk conditions also receive benefit from vaccination in the form of decreased rates of influenza illness, decreased work absenteeism, and decreased need for medical visits and medication, including antibiotics. Further, 50 years is an age when other preventive services begin and when routine assessment of vaccination and other preventive services has been recommended.¹

Persons who can transmit influenza to those at high risk

Persons who are clinically or subclinically infected can transmit influenza virus to persons at high risk for complications from influenza. Decreasing transmission of influenza from care-givers and household contacts to persons at high risk might reduce influenza-related deaths among persons at high risk. Evidence from two studies indicates that vaccination of health-care personnel is associated with decreased deaths among nursing home patients. Health-care workers should be vaccinated against influenza annually. Facilities that employ health-care workers are strongly encouraged to provide vaccine to workers by using approaches that maximize immunization rates. This will protect health-care workers, their patients, and communities, and will improve prevention, patient safety, and reduce disease burden. Health-care workers' influenza immunization rates should be regularly measured and reported. Although rates of health-care worker vaccination are typically <40%, with moderate effort, organized campaigns can attain higher rates of vaccination among this population.¹

The following groups should be vaccinated:¹

1. Physicians, nurses, and other personnel in both hospital and outpatient-care settings, including medical emergency response workers (e.g. paramedics and emergency medical technicians).¹
2. Employees of nursing homes and chronic-care facilities who have contact with patients or residents.¹
3. Employees of assisted living and other residences for persons in groups at high risk.¹
4. Persons who provide home care to persons in groups at high risk.¹
5. Household contacts (including children) of persons in groups at high risk.¹

In addition, because children aged 0-23 months are at increased risk for influenza-related hospitalization, vaccination is recommended for their household contacts and out-of-

home caregivers, particularly for contacts of children aged 0-5 months because influenza vaccines have not been approved by the U.S. Food and Drugs Administration (FDA) for use among children aged <6 months.¹

Immunization Of Other Groups

General population

In addition to the groups for which annual influenza vaccination is recommended, physicians should administer influenza vaccine to any person who wishes to reduce the likelihood of becoming ill with influenza. See **INDICATIONS AND USAGE**, and **WARNINGS** sections. Persons who provide essential community services should be considered for vaccination to minimize disruption of essential activities during influenza outbreaks. Students or other persons in institutional settings (e.g., those who reside in dormitories) should be encouraged to receive vaccine to minimize the disruption of routine activities during epidemics.¹

Pregnant women

Influenza-associated excess deaths among pregnant women were documented during the pandemics of 1918-1919 and 1957-1958. Case reports and limited studies also indicate that pregnancy can increase the risk for serious medical complications of influenza. An increased risk might result from increases in heart rate, stroke volume and oxygen consumption; decreases in lung capacity; and changes in immunologic function during pregnancy. A study of the effect of influenza during 17 interpandemic influenza seasons demonstrated that the relative risk for hospitalization for selected cardiorespiratory conditions among pregnant women enrolled in Medicaid increased from 1.4 during weeks 14-20 of gestation to 4.7 during weeks 37-42 in comparison with women who were 1-6 months postpartum. Women in their third trimester of pregnancy were hospitalized at a rate (i.e., 250 per 100,000 pregnant women) comparable with that of nonpregnant women who had high-risk medical conditions. Researchers estimated that an average of 1-2 hospitalizations can be prevented for every 1,000 pregnant women vaccinated.¹ Because of the increased risk for influenza-related complications, women who will be pregnant during the influenza season should be vaccinated. Vaccination can occur in any trimester.¹

One study of influenza vaccination of >2,000 pregnant women demonstrated no adverse fetal effects associated with influenza vaccine.

The majority of influenza vaccine distributed in the United States contains thimerosal, a mercury-containing compound, as a preservative. Thimerosal has been used in U.S. vaccines since the 1930s. No scientifically conclusive evidence exists of harm from exposure to thimerosal preservative-containing vaccine.¹ The risks of severe illness from influenza infection are elevated among pregnant women and young children, and both groups benefit from vaccination by preventing illness and death from influenza.¹ Controlled studies on **FLUVIRIN®** have not been conducted to demonstrate safety in pregnant women.

The clinical judgment of the attending physician should prevail at all times in determining whether to administer the vaccine to a pregnant woman (see PRECAUTIONS, Use in Pregnancy).

Breast feeding mothers

Influenza vaccine does not affect the safety of mothers who are breastfeeding or their infants. Breastfeeding does not adversely affect the immune response and is not a contraindication for vaccination.¹

Persons infected with human immunodeficiency virus (HIV)

Limited information is available regarding the frequency and severity of influenza illness or the benefits of influenza vaccination among persons with human immunodeficiency virus (HIV) infection. However, a retrospective study of young and middle-aged women enrolled in Tennessee's Medicaid program determined that the attributable risk for cardiopulmonary hospitalizations among women with HIV infection was higher during influenza seasons than during the peri-influenza periods. The risk for hospitalization was higher for HIV-infected women than for women with other well-recognized high-risk conditions, including chronic heart and lung diseases. Another study estimated that the risk for influenza-related death was 9.4-14.6 per 10,000 persons with acquired immunodeficiency syndrome (AIDS) compared with 0.09-0.10 per 10,000 among all persons aged 25-54 years and 6.4-7.0 per 10,000 among persons aged ≥ 65 years. Other reports indicate that influenza symptoms might be prolonged and the risk for complications from influenza increased for certain HIV-infected persons.¹

Influenza vaccination has been demonstrated to produce substantial antibody titers against influenza among vaccinated HIV-infected persons who have minimal AIDS-related symptoms and high CD4+ T-lymphocyte cell counts. A limited, randomized, placebo-controlled trial determined that influenza vaccine was highly effective in preventing symptomatic, laboratory-confirmed influenza infection among HIV-infected persons with a mean of 400 CD4+ T-lymphocyte cells/mm³; a limited number of persons with CD4+ T-lymphocyte cell counts of <200 were included in that study. A nonrandomized study among HIV-infected persons determined that influenza vaccination was most effective among persons with >100 CD4+ cells and among those with $<30,000$ viral copies of HIV type 1/mL.¹ Among persons who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, influenza vaccine might not induce protective antibody titers; a second dose of vaccine does not improve the immune response in these persons.¹

One study determined that HIV RNA (ribonucleic acid) levels increased transiently in one HIV-infected person after influenza infection. Studies have demonstrated a transient (i.e., 2- to 4-week) increase in replication of HIV-1 in the plasma or peripheral blood mononuclear cells of HIV-infected persons after vaccine administration. Other studies using similar laboratory techniques have not documented a substantial increase in the replication of HIV. Deterioration of CD4+ T-lymphocyte cell counts or progression of HIV disease have not been demonstrated among HIV-infected persons after influenza vaccination compared with unvaccinated persons. Limited information is available concerning the effect of antiretroviral therapy on increases in HIV RNA levels after either natural influenza infection or influenza vaccination. Because influenza can result in serious illness and because influenza vaccination can result in the production of protective antibody titers, vaccination will benefit HIV-infected persons, including HIV-infected pregnant women.¹

Travelers

The risk for exposure to influenza during travel depends on the time of year and destination. In the tropics, influenza can occur throughout the year. In the temperate regions of the Southern Hemisphere, the majority of influenza activity occurs during April-September. In temperate climate zones of the Northern and Southern Hemispheres, travelers also can be exposed to influenza during the summer, especially when traveling as part of large organized tourist groups (e.g., on cruise ships) that include persons from areas of the world where influenza viruses are circulating. Persons at high risk for complications of influenza who were not vaccinated with influenza vaccine during the preceding fall or winter should consider receiving influenza vaccine before travel if they plan to a) travel to the tropics; b) travel with organized tourist groups at any time of year; or c) travel to the Southern Hemisphere during April-September. No information is available regarding the benefits of revaccinating persons before summer travel who were already vaccinated in the preceding fall. Persons at high risk who received the previous season's vaccine before travel should be revaccinated with the current vaccine in the following fall or winter. Persons aged ≥ 50 years and others at high risk should consult with their physicians before embarking on travel during the summer to discuss the symptoms and risks for influenza.¹

Healthy Young Children

Studies indicate that rates of hospitalization are higher among young children than older children when influenza viruses are in circulation. The increased rates of hospitalization are comparable with rates for other groups considered at high risk for influenza-related complications. However, the interpretation of these findings has been confounded by co-circulation of respiratory syncytial viruses, which are a cause of serious respiratory viral illness among children and which frequently circulate during the same time as influenza viruses. Two recent studies have attempted to separate the effects of respiratory syncytial viruses and influenza viruses on rates of hospitalization among children who do not have high-risk conditions.¹ Both studies reported that otherwise healthy children aged < 2 years, and possibly children aged 2-4 years, are at increased risk for influenza-related hospitalization compared with older healthy children. Among the Tennessee Medicaid population during 1973-1993, healthy children aged 6 months- < 3 years had rates of influenza-associated hospitalization comparable with or higher than rates among children aged 3-14 years with high risk conditions.¹ Another Tennessee study reported a hospitalization rate per year of 3-4 per 1,000 healthy children aged < 2 years for laboratory confirmed influenza.¹

Because children aged 6-23 months are at substantially increased risk for influenza-related hospitalizations, ACIP recommends vaccination of all children in this age group. ACIP continues to strongly recommend influenza vaccination of persons aged ≥ 6 months who have high-risk medical conditions.¹

The current inactivated influenza vaccine is not approved by FDA for use among children aged < 6 months, the pediatric group at greatest risk for influenza-related complications.¹ Vaccinating their household contacts and out-of-home caregivers might decrease the probability of influenza infection among these children.

Persons Who Should Not Be Vaccinated

Inactivated influenza vaccine should not be administered to persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine

without first consulting a physician¹ (see **Contraindications, Warnings, Adverse Reactions - Systemic Reactions**). Prophylactic use of antiviral agents is an option for preventing influenza among such persons.¹ However, persons who have a history of anaphylactic hypersensitivity to vaccine components but who are also at high risk for complications from influenza can benefit from vaccine after appropriate allergy evaluation and desensitization.¹ Persons with acute febrile illness usually should not be vaccinated until their symptoms have abated. However, minor illnesses with or without fever do not contraindicate the use of influenza vaccine, particularly among children with mild upper respiratory tract infection or allergic rhinitis.¹

TIMING OF ANNUAL INFLUENZA VACCINATION

ACIP recommends that vaccine campaigns conducted in October should focus their efforts primarily on persons at increased risk for influenza complications and their contacts, including health-care workers. Campaigns conducted in November and later should continue to vaccinate persons at high risk and their contacts, but also vaccinate other persons who wish to decrease their risk for influenza infection. Vaccination efforts for all groups should continue into December and beyond.¹

Vaccination in October and November

The optimal time to vaccinate is usually during October-November. ACIP recommends that vaccine providers focus their vaccination efforts in October and earlier primarily on persons aged ≥ 50 years, persons aged < 50 years at increased risk for influenza-related complications, household contacts of persons at high risk (including out-of-home caregivers and household contacts of children aged 0-23 months), and health-care workers.¹ Vaccination of children aged < 9 years who are receiving vaccine for the first time should also begin in October or earlier because those persons need a booster dose 1 month after the initial dose.¹ Efforts to vaccinate other persons who wish to decrease their risk for influenza infection should begin in November; however, if such persons request vaccination in October, vaccination should not be deferred.

Vaccination in December and Later

After November, many persons who should, or want to receive influenza vaccine remain unvaccinated. In addition, substantial amounts of vaccine have remained unused during three of the past four influenza seasons. To improve vaccine coverage, influenza vaccine should continue to be offered in December and throughout the influenza season as long as vaccine supplies are available, even after influenza activity has been documented in the community.¹ In the United States, seasonal activity can begin to increase as early as October or November, but influenza activity has not reached peak levels in the majority of recent seasons until late December - early March. Therefore, although the timing of influenza activity can vary by region, vaccine administered after November is likely to be beneficial in the majority of influenza seasons. Adults develop peak antibody protection against influenza infection 2 weeks after vaccination.¹

Vaccination Before October

To avoid missed opportunities for vaccination of persons at high risk for serious complications, such persons should be offered vaccine beginning in September during routine health-care visits or during hospitalizations, if vaccine is available¹. In facilities

housing older persons (e.g., nursing homes), vaccination before October typically should be avoided because antibody levels in such persons can begin to decline within a limited time after vaccination.¹ In addition, children aged <9 years who have not been previously vaccinated and who need 2 doses before the start of the influenza season can receive their first dose in September or earlier.¹

Timing of Organized Vaccination Campaigns

Persons planning substantial organized vaccination campaigns should consider scheduling these events after mid-October because the availability of vaccine in any location cannot be ensured consistently in early fall.¹ Scheduling campaigns after mid-October will minimize the need for cancellations because vaccine is unavailable. Campaigns conducted before November should focus efforts on vaccination of persons aged ≥50 years, persons aged <50 years at increased risk for influenza-related complications, health-care workers, and household contacts of persons at high-risk (including children aged 0-23 months) to the extent feasible.¹

CONTRAINDICATIONS

INFLUENZA VIRUS IS PROPAGATED IN EGGS FOR THE PREPARATION OF INFLUENZA VIRUS VACCINE. THUS, THIS VACCINE SHOULD NOT BE ADMINISTERED TO ANYONE WITH A HISTORY OF HYPERSENSITIVITY (ALLERGY) TO CHICKEN EGGS, CHICKEN, CHICKEN FEATHERS OR CHICKEN DANDER.

THE VACCINE IS ALSO CONTRAINDICATED IN INDIVIDUALS HYPERSENSITIVE TO ANY COMPONENT OF THE VACCINE INCLUDING THIMEROSAL (A MERCURY DERIVATIVE) (SEE ADVERSE REACTIONS). EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF THE VACCINE.

IMMUNIZATION SHOULD BE DELAYED IN PERSONS WITH AN ACTIVE NEUROLOGICAL DISORDER CHARACTERIZED BY CHANGING NEUROLOGICAL FINDINGS, BUT SHOULD BE CONSIDERED WHEN THE DISEASE PROCESS HAS BEEN STABILIZED.

THE OCCURRENCE OF ANY NEUROLOGICAL SYMPTOMS OR SIGNS FOLLOWING ADMINISTRATION OF ANY VACCINE IS A CONTRAINDICATION TO FURTHER USE.

THE VACCINE SHOULD NOT BE ADMINISTERED TO PERSONS WITH ACUTE FEBRILE ILLNESSES UNTIL THEIR TEMPORARY SYMPTOMS AND/OR SIGNS HAVE ABATED.

The clinical judgment of the attending physician should prevail at all times.

WARNINGS

Influenza Virus Vaccine should not be given to individuals with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection unless, in the judgment of the physician, the potential benefits clearly outweigh the risk of administration.

Patients with impaired immune responsiveness, whether due to the use of immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites, alkylating agents, and cytotoxic agents), a genetic defect, human immunodeficiency virus (HIV) infection, or other causes, may have a reduced antibody response in active immunization procedures.

As with any vaccine, immunization with Influenza Virus Vaccine may not result in seroconversion of all individuals given the vaccine.

Special care should be taken to prevent injection into a blood vessel.

PRECAUTIONS

General

1. PRIOR TO ADMINISTRATION OF ANY DOSE OF INFLUENZA VIRUS VACCINE, THE PARENT, GUARDIAN, OR ADULT PATIENT SHOULD BE ASKED ABOUT THE RECENT HEALTH STATUS, MEDICAL AND IMMUNIZATION HISTORY OF THE PATIENT TO BE IMMUNIZED IN ORDER TO DETERMINE THE EXISTENCE OF ANY CONTRAINDICATION TO IMMUNIZATION WITH INFLUENZA VIRUS VACCINE (see **CONTRAINDICATIONS, WARNINGS**).

2. BEFORE ADMINISTRATION OF ANY BIOLOGICAL, THE PHYSICIAN SHOULD TAKE ALL PRECAUTIONS KNOWN FOR PREVENTION OF ALLERGIC OR ANY OTHER SIDE REACTIONS. This should include: a review of the patient's history regarding possible sensitivity, the ready availability of epinephrine 1:1,000 and other appropriate agents used for control of immediate allergic reactions, and a knowledge of the recent literature pertaining to use of the biological concerned, including the nature of side effects and adverse reactions that may follow its use.

3. A separate sterile syringe and needle or a sterile disposable unit must be used for each individual patient to prevent transmission of infectious agents from one person to another.

Information for the patient

PRIOR TO ADMINISTRATION OF THIS VACCINE, HEALTH CARE PERSONNEL SHOULD INFORM THE PARENT, GUARDIAN, OR ADULT PATIENT OF THE BENEFITS AND RISKS OF IMMUNIZATION AGAINST INFLUENZA.

Drug interactions

Although influenza immunization can inhibit the clearance of warfarin and theophylline, studies have not established any adverse clinical effects attributable to these drugs in patients receiving influenza vaccine.

Use in pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with Influenza Virus Vaccine (FLUVIRIN®). It is also not known whether Influenza Virus Vaccine (FLUVIRIN®) can cause fetal harm when administered to a pregnant woman or can affect reproduction

capacity. Influenza Virus Vaccine (**FLUVIRIN®**) should be given to a pregnant woman only if clearly needed.

See **IMMUNIZATION OF OTHER GROUPS, Pregnant Women.**

The clinical judgment of the attending physician should prevail at all times in determining whether to administer Influenza Virus Vaccine to a pregnant woman.

Pediatric use

The safety and immunogenicity of **FLUVIRIN®** have been established in the age group 4 years to 16 years. The use of **FLUVIRIN®** in these age groups is supported by evidence from adequate and well-controlled studies of **FLUVIRIN®** in adults that demonstrate the immunogenicity of **FLUVIRIN®**.

The safety and immunogenicity of **FLUVIRIN®** have not been established in children < 4 years of age.

See **CLINICAL PHARMACOLOGY** section for additional information.

Geriatric use

Of the total number of subjects in clinical studies of **FLUVIRIN®** (n = 632), 37% were 65 and over, while 2.4% were 75 and over. No overall differences in safety or immunogenicity were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

See **CLINICAL PHARMACOLOGY** section for additional information.

ADVERSE REACTIONS

When educating patients regarding potential side-effects, clinicians should emphasize that a) inactivated influenza vaccine contains noninfectious killed viruses and cannot cause influenza; and b) coincidental respiratory disease unrelated to influenza vaccination can occur after vaccination.¹

Local reactions

In placebo-controlled studies among adults, the most frequent side effect of vaccination is soreness at the vaccination site (affecting 10%-64% of patients) that lasts <2 days. These local reactions typically are mild and rarely interfere with the person's ability to conduct usual daily activities.¹ One blinded, randomized, cross-over study among 1,952 adults and children with asthma, demonstrated that only body aches were reported more frequently after inactivated influenza vaccine (25.1%) than placebo-injection (20.8%).¹ One study¹ reported 20%-28% of children with asthma aged 9 months-18 years with local pain and swelling and another study¹ reported 23% of children aged 6 months – 4 years with chronic heart or lung disease had local reactions. A different study¹ reported no difference in local reactions among 53 children aged 6 months-6 years with high risk medical conditions or among 305 healthy children aged 3-12 years in a placebo-controlled trial of inactivated influenza vaccine. In a study of 12 children aged 5-32 months, no substantial local or systemic reactions were noted.¹

Systemic reactions

Fever, malaise, myalgia, and other systemic symptoms can occur after vaccination with inactivated vaccine and most often affect persons who have had no prior exposure to the

influenza virus antigens in the vaccine (e.g., young children). These reactions begin 6-12 hours after vaccination and can persist for 1 - 2 days. Recent placebo-controlled trials demonstrate that among older persons and healthy young adults, administration of split-virus influenza vaccine is not associated with higher rates of systemic symptoms (e.g., fever, malaise, myalgia and headache) when compared with placebo injections.¹

Less information from published studies is available for children, compared with adults. However, in a randomized cross-over study among both children and adults with asthma, no increase in asthma exacerbations was reported for either age group. An analysis of 215,600 children aged <18 years and 8,476 children aged 6-23 months enrolled in one of five health maintenance organizations reported no increase in biologically plausible medically attended events during the 2 weeks after inactivated influenza vaccination, compared with control periods 3-4 weeks before and after vaccination.¹

In a study of 791 healthy children¹, postvaccination fever was noted among 11.5% of children aged 1-5 years, 4.6% among children aged 6-10 years, and 5.1% among children aged 11-15 years. Among children with high risk medical conditions, one study of 52 children aged 6 months-4 years reported fever among 27% and irritability and insomnia among 25%¹; a study among 33 children aged 6-18 months reported that one child had irritability and one had a fever and seizure after vaccination.¹ No placebo comparison was made in these studies. However, in pediatric trials of A/New Jersey/76 swine influenza vaccine, no difference was reported between placebo and split-virus vaccine groups in febrile reactions after injection, although the vaccine was associated with mild local tenderness or erythema.¹ Limited data regarding potential adverse events after influenza vaccination are available from the Vaccine Adverse Event Reporting System (VAERS). During January 1, 1991- January 23, 2003, VAERS received 1,072 reports of adverse events among children aged <18 years, including 174 reports of adverse events among children aged 6-23 months. The number of influenza vaccine doses received by children during this time period is unknown. The most frequently reported events among children were fever, injection-site reactions, and rash (unpublished data, CDC, 2003).¹ Because of the limitations of spontaneous reporting systems, determining causality for specific types of adverse events, with the exception of injection-site reactions, is usually not possible by using VAERS data alone.¹

Health care professionals should promptly report all clinically significant adverse events after influenza vaccination of children to VAERS even if the health care professional is not certain that the vaccine caused the event. The Institute of Medicine has specifically recommended reporting of potential neurologic complications (e.g., demyelinating disorders such as Guillain-Barré [GBS] syndrome), although no evidence exists of a causal relationship between influenza vaccine and neurologic disorders in children.¹

Immediate - presumably allergic - reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) rarely occur after influenza vaccination. These reactions probably result from hypersensitivity to certain vaccine components; the majority of reactions probably are caused by residual egg protein. Although influenza vaccines contain only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Persons who have had hives, or swelling of the lips or tongue, or who have experienced acute respiratory distress or collapse after eating eggs should consult a physician for appropriate evaluation to help determine if vaccine should be administered. Persons who have documented immunoglobulin E (IgE)-mediated hypersensitivity to eggs - including those who have

had occupational asthma or other allergic responses to egg protein - might also be at increased risk for allergic reactions to influenza vaccine, and consultation with a physician should be considered. Protocols have been published for safely administering influenza vaccine to persons with egg allergies.¹

Hypersensitivity reactions to any vaccine component can occur. Although exposure to vaccines containing thimerosal can lead to induction of hypersensitivity, the majority of patients do not have reactions to thimerosal when it is administered as a component of vaccines, even when patch or intradermal tests for thimerosal indicate hypersensitivity. When reported, hypersensitivity to thimerosal usually has consisted of local, delayed hypersensitivity reactions.¹

Guillain-Barré Syndrome

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS). Among persons who received the swine influenza vaccine in 1976, the rate of GBS was <10 cases/1 million persons vaccinated. The risk for influenza vaccine-associated GBS is higher among persons aged ≥ 25 years than persons <25 years. Evidence for a causal relationship of GBS with subsequent vaccines prepared from other influenza viruses is unclear. Obtaining strong epidemiologic evidence for a possible limited increase in risk is difficult for such a rare condition as GBS, which has an annual incidence of 10-20 cases per million adults. More definitive data probably will require the use of other methodologies (e.g., laboratory studies of the pathophysiology of GBS).¹

During three of four influenza seasons studied during 1977-1991, the overall relative risk estimates for GBS after influenza vaccination were slightly elevated but were not statistically significant in any of these studies. However, in a study of the 1992-1993 and 1993-1994 seasons, the overall relative risk for GBS was 1.7 (95% confidence interval = 1.0-2.8; $p=0.04$) during the 6 weeks after vaccination, representing approximately one additional case of GBS per million persons vaccinated. The combined number of GBS cases peaked 2 weeks after vaccination. Thus, investigations to date indicate no substantial increase in GBS associated with influenza vaccines (other than the swine influenza vaccine in 1976) and that, if influenza vaccine does pose a risk, it is probably slightly more than one additional case per million persons vaccinated. Cases of GBS after influenza infection have been reported, but no epidemiologic studies have documented such an association. Substantial evidence exists that multiple infectious illnesses, most notably *Campylobacter jejuni*, as well as upper respiratory tract infections in general, are associated with GBS.¹

Even if GBS were a true side effect of vaccination in the years after 1976, the estimated risk for GBS of approximately one additional case per million persons vaccinated is substantially less than the risk for severe influenza, which could be prevented by vaccination among all age groups, especially persons aged ≥ 65 years and those who have medical indications for influenza vaccination. The potential benefits of influenza vaccination in preventing serious illness, hospitalization, and death substantially outweigh the possible risks for experiencing vaccine-associated GBS. The average case-fatality ratio for GBS is 6% and increases with age. No evidence indicates that the case-fatality ratio for GBS differs among vaccinated persons and those not vaccinated.¹

The incidence of GBS in the general population is low, but persons with a history of GBS have a substantially greater likelihood of subsequently experiencing GBS than persons

without such a history. Thus, the likelihood of coincidentally experiencing GBS after influenza vaccination is expected to be greater among persons with a history of GBS than among persons with no history of this syndrome. Whether influenza vaccination specifically might increase the risk for recurrence of GBS is unknown; therefore, avoiding vaccinating persons who are not at high risk for severe influenza complications and who are known to have experienced GBS within six weeks after a previous influenza vaccination is prudent. Although data are limited, for the majority of persons who have a history of GBS and who are at high risk for severe complications from influenza, the established benefits of influenza vaccination justify yearly vaccination.¹

Other neurological disorders, including encephalopathies not defined as GBS, have been temporally associated with influenza immunization, but no causal link has been established.

DOSAGE AND ADMINISTRATION

For Intramuscular Use Only. DO NOT INJECT INTRAVENOUSLY.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration (see **DESCRIPTION**).

Vaccine prepared for a previous influenza season should not be administered to provide protection for the current season.

Although Influenza Virus Vaccine often contains one or more antigens used in previous years, immunity declines during the year following immunization. Therefore, a history of immunization in any previous year with a vaccine containing one or more antigens included in the current vaccine does NOT preclude the need for reimmunization for the 2006-2007 influenza season in order to provide optimal protection.

See **TIMING OF ANNUAL INFLUENZA VACCINATION** for information regarding the optimal time of administration of this vaccine.

During recent decades, data on influenza vaccine immunogenicity and side effects have generally been obtained when vaccine has been administered intramuscularly. Because recent influenza vaccines have not been adequately evaluated when administered by other routes, the intramuscular route is recommended. Adults and older children should be vaccinated in the deltoid muscle. Infants and young children should be vaccinated in the anterolateral aspect of the thigh.¹

Before immunization, the skin over the site to be injected should be cleansed with a suitable germicide. After insertion of the needle, aspirate to help avoid inadvertent injection into a blood vessel.

Dosage recommendations vary according to age group, as follows:

Age Group	Dose	No. of Doses (See below for details)
< 4 years	Vaccine should not be used	
4 to 8 years	0.5 mL	1 or 2 Doses
9 years and older	0.5 mL	1 Dose

Among previously unvaccinated children aged <9 years, 2 doses administered at least 1 month apart are recommended for satisfactory antibody responses. If possible, the second dose should be administered before December. If a child aged <9 years receiving

vaccine for the first time does not receive a second dose of vaccine within the same season, only one dose of vaccine should be administered the following season. Two doses are not required at that time. Among adults, studies have indicated little or no improvement in antibody response when a second dose is administered during the same season.¹

Because of their decreased potential for causing febrile reactions, only split-virus vaccines should be used for children aged <13 years. The vaccines might be labelled as “split”, “subvirion”, or “purified-surface-antigen” vaccine.¹

The 0.5 mL preservative free pre-filled syringe presentation is intended for single use only and must not be used in more than one individual.

0.25 mL doses (indicated by a graduation line) should not be used.

Do not reuse empty syringe.

Chiron Vaccines Limited does not recommend the use of needleless injectors for administration of **FLUVIRIN®**.

Simultaneous administration of other vaccines, including childhood vaccines

Inactivated influenza vaccine coadministration has been evaluated systematically only among adults with pneumococcal polysaccharide vaccine.¹

No studies regarding the simultaneous administration of inactivated influenza vaccine and other childhood vaccines have been conducted. However, inactivated vaccines usually do not interfere with the immune response to other inactivated or live vaccines.¹ However, physicians may prefer not to administer influenza vaccine within 3 days of administration of pertussis containing vaccines.

HOW SUPPLIED

NDC 66521-109-01; 0.5 mL pre filled syringe (preservative-free formulation; contains trace amounts of residual thimerosal, ≤ 0.98 mcg mercury per 0.5 mL dose).

STORAGE

DO NOT FREEZE. STORE REFRIGERATED, AWAY FROM FREEZER COMPARTMENT, AT 2°C to 8°C (36°F to 46°F).

FROZEN/PREVIOUSLY FROZEN PRODUCT SHOULD NOT BE USED.

Vaccine must be transported under refrigeration temperatures.

REFERENCES

1. Centers for Disease Control and Prevention. Prevention and Control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2004; 53 (Early Release): [1-40].

IMPORTANT INFORMATION for Group Immunization Programs: If this vaccine is to be used in an immunization program sponsored by any organization WHERE A TRADITIONAL PHYSICIAN/PATIENT RELATIONSHIP DOES NOT EXIST, each recipient (or legal guardian) must be made aware of the benefits and risks of immunization, and informed consent should be obtained from the recipient (or legal guardian) before immunization. Risks of immunization are summarized in the current

CHIRON VACCINES LIMITED

labeling. PLEASE CONTACT CDC, or your local State Department of Health to obtain Important Information about Influenza and a sample Influenza Consent Form.

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